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ATTENTIONAL CONTROL IN DEPRESSION: A TRANSLATIONAL AFFECTIVE NEUROSCIENCE APPROACH

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ABSTRACT

Translational research refers to the application of basic science to address clinical problems and to acquire knowledge that can be used to guide and refine clinical practice. This special issue seeks to explore and integrate some of the most promising findings offered by recent cognitive and affective neuroscience studies to fill the gap between basic and applied research thereby heightening our understanding of vulnerability for depression. The studies presented in this special issue focus specifically on attentional processes. We solicited contributions from leading researchers who are involved in basic cognitive and neuroscience research investigating processes underlying depression-related disturbances in emotion processing. In this introductory paper, we present an integrative overview to demonstrate how the specific contributions of this special issue might be valuable for translational research.

KEY WORDS: depression, affective neuroscience, translational research, attention

THE PROBLEM OF DEPRESSION VULNERABILITY

Depression is a common and severe psychiatric illness that, despite immense research efforts, poses important challenges for prevention and treatment. Although many psychotherapeutic and pharmacological treatments have been developed, recent meta-analyses report rather small effect sizes (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, in press; Kirsch, Deacon, Huedo-Medina, Scoboria, Moore, & Johnson, 2008; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Moreover, within the group of depressed individuals who do show initial improvement in response to treatment, a large proportion will experience relapse within a number of years after treatment completion and depression becomes a recurrent problem (Goodwin, Jacobi, Bittner, & Wittchen, 2006). These disappointing results provide an important impetus for researchers and clinicians to join forces in trying to better understand and treat this debilitating disorder. Indeed, it might be crucial to rethink our current approaches to understanding and treating depression by integrating basic and clinical research and refining interventions accordingly.

Depression is a mood disorder characterized by sustained negative affect and loss of positive affect. First onsets of depression are frequently linked to the experience of stressful life events. Integrating basic research on biological stress reactivity, cognition, and on the relation of cognitive processes to stress recovery, affect generation and regulation, therefore promises to improve our understanding and treatment of this debilitating disorder. Contemporary research on the interaction of cognition and emotion, often from an affective neuroscience perspective, has provided important insights into the functioning of normative as well as disrupted emotion networks in the brain. Recently, models have been developed that elucidate the manner in which affect impringes the attentional control system and vica versa (Taylor & Fragopanagos, 2005). These studies have helped improve our understanding of the role of attention engagement and disengagement and other forms of cognitive control in

emotion generation and regulation. Importantly, these models have helped to identify cognitive processes, often operating on an automatic level, that may play a critical role in the generation of affective responses and impair people's ability to repair the ensuing affect. This research has also helped to identify brain regions and networks associated with emotion processing and cognitive control and the relation of these brain regions to other biological systems critical in regulating stress responding such as the Hypothalamic- Pituitary Adrenal-axis (HPA-axis). Basic science research on the interaction of cognition and emotion, therefore,may help to increase our understanding of individual differences in the ability to disengage from the elaborative processing of negative cognitions after confrontation with stressors, a core problem in depression. Contemporary research on the interaction of cognition and emotion has also moved beyond merely demonstrating that affective states and traits are associated with biased cognitive processing, to investigating the causal mechanisms underlying affect regulation and emotional vulnerability, an important step in exploring possibilities for modification (see Mathews & MacLeod, 2005, for a recent review). Brain imaging studies, for example, have outlined changes in neural response patterns such as increased activations in limbic regions and reduced activations in prefrontal cortex that seem to be present in high-risk individuals even before the first episode of depression is experienced (e.g. Monk et al., 2008). Our most effective interventions such as cognitive-behavioral therapy (CBT) focus on modifying maladaptive cognitions and cognitive biases. Remarkably, however, these interventions have undergone few modifications in the last 50 years and the theoretical foundations of CBT for depression are still largely rooted in Beck's cognitive theory proposed in the 1960s (e.g., Beck, 1976). At the same time, we have seen an impressive increase in experimental psychopathology research over the past decades, which has led to important improvements in our models of depression and in our thinking about biological and psychological factors that increase the risk for the onset of this disorder and

play a critical role in the maintenance of depressive episodes (Beck, 2008). These findings, however, have not been translated into more efficient treatments.

We therefore consider the interplay between basic research and clinical research to be of crucial importance in improving our understanding of depression and its treatment. An important goal of this special issue is to bring together some of the key developments in basic science on cognition and emotion and its relevance to the understanding and treatment of depressive disorders. For this purpose we will use a translational affective neuroscience approach.

TRANSLATIONAL AFFECTIVE NEUROSCHENCE

Translational research refers to the application of basic science to address clinical problems and to acquire knowledge that can be used to guide and refine clinical practice. The present special issue seeks to explore and integrate some of the most promising findings offered by new studies to fill the gap between basic and applied research thereby heightening our understanding of vulnerability for depression and ultimately improving treatment and prevention. In this special issue, we solicited contributions from leading researchers who are involved in basic cognitive and affective neuroscience research. This special issue focuses specifically on attentional problems in depression. In recent years evidence has been accumulated to suggest that specific attentional problems are observed when depressed and dysphoric people process affective material (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Leyman, De Raedt, Schacht & Koster, 2007). Specifically, depression is associated with difficulties in disengaging attention from mood-congruent material and with difficulties terminating elaborative processing of such material. Given the crucial role of attention in both general cognitive functioning such as executive control (Engle, 2002) and working memory (Hasher & Zacks, 1979) as well as emotion-relevant functioning such as emotional reactivity

(MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002), emotion regulation (Koole, 2009) and depressive symptoms (Beevers & Carver, 2003), it seems warranted to further examine attentional factors in depression. The aim of this special issue of *Cognitive, Behavioral and Affective Neuroscience* is to present an overview of basic research from different perspectives on attentional control that can provide crucial input to the development of innovative treatment and prevention strategies.

There are numerous aspects of intervention that could profit from affective neuroscience insights into the mechanisms underlying the generation and regulation of affect. Specifically, a better understanding of affect generation and regulation and of cognitive and neural mechanisms underlying pharmacological and psychological treatments could help (1) integrating these interventions in a theory-based way; (2) refining intervention strategies; (3) matching patients to specific interventions; (4) tackling the problem of non-response to pharmacological or psychological treatments and; (5) predicting and preventing relapse after initially successful treatments.

To facilitate a translational affective neuroscience approach, several lines of research are required including but not limited to affective neuroscience research investigating the processes involved in depression-related disturbances in emotion processing and the influence of these disturbances on emotional reactivity, emotion regulation, and depressive symptoms. Moreover, integrative theoretical models are needed to help understand the emerging findings and to guide future research. In what follows, we will present an overview of how the specific contributions of this special issue might be valuable for translational research.

PROCESSES UNDERLYING VULNERABILITY FOR DEPRESSION

A first requirement for understanding the nature of disrupted attentional and biological processes in depression is to obtain a detailed picture of the interplay between emotion

processing and attention in the brain. The amygdala is a limbic structure that is a central part of many neural models of emotion that has also been implicated in depression risk, yet its role in emotion generation and regulation remains open to debate. Using sophisticated methodology, Pourtois, Spinelli, Seeck and Vuillemier (2010, in this issue) recorded intracranial local field potentials from the intact left lateral amygdala in an epileptic patient to investigate neural responses to fearful faces presented in attended or unattended locations. These authors demonstrated an early effect of the presentation of emotional material in the left amygdala prior to, and independent of, attentional modulation. When attention was directed towards or away from fearful faces, at later stages of processing, they observed modulation of differential emotional responses, suggesting separate effects of emotion and attention on amygdala activation. These results underscore the critical role of the amygdala in emotion processing, responsible for detecting, generating, and maintaining emotions (Phan, Wager, Taylor, & Liberzon, 2004) and suggest that this structure is important in early and later stages of the processing of emotional material. Further support for a close relation among attentional processing of emotional material and variations in neurobiological systems comes from an attention paradigm used by Ellenbogen, Robyn, Carson and Pishva (2010, in this issue). Attentional shifting during trials in which masked angry faces were presented predicted changes in cortisol release during a stress induction, suggesting that early automatic processing of emotional stimuli is related to the regulation of the HPA axis stress response. Taken together, these data are indicative of a close relation between the physiological stress response and left amygdala activity during the processing of threatening information.

Closely related to findings from these basic science studies, ever more evidence shows that a history of early exposure to stressors such as childhood neglect and attachment problems may contribute to changes in neurobiological systems such as the Hypothalamic Pituitary Adrenal (HPA) axis, brain structure and function, for example the hippocampus, and

neurotransmitter systems, causing an increased susceptibility for affective disorders (e.g. Gerra et al., 2009). The relation between this increased neurobiological vulnerability and depression might be mediated by dysfunctional emotion processing. Indeed, childhood neglect has been shown to influence emotion processing in a negative way (e.g. Masten et al., 2008). Maheu, Dozier, Peloso, Lau, Ackerman, Pine and Ernst (2010, in this issue) integrate research on cognitive and biological vulnerability in an fMRI study investigating whether specific brain dysfunctions could underlie the relation between exposure to early stressors and sensitivity to threat cues. Youths with a history of early caregiver deprivation and emotional neglect demonstrated significantly greater left amygdala and left anterior hippocampus activation during the processing of threatening stimuli. These findings suggest a specific scarring effect in limbic structures that may result from early exposure to stressors and may set the stage for increased vulnerability to emotional disorders.

Implications of these observations for translational research are nicely illustrated in the review by Browning, Holmes, and Harmer (2010, in this issue). These authors discuss evidence that attentional biases are responsive to the administration of pharmacological agents in non-clinical populations. Although studies involving clinical populations may indicate that the findings are secondary to improved clinical status rather than being a treatment effect, their literature review suggests that pharmacological interventions affect an initial bias operating at an early stage of the processing of emotional material potentially related to an amygdala based stimulus appraisal system. In contrast, psychological interventions affect attention at later stages of cognitive processing, related to anterior cingulate cortex (ACC) and lateral prefrontal cortex activity. Taken together, results obtained from these reviews and results obtained from the previously discussed experimental data showing differences in attention biases between early and late processing stages in depression can set the stage for a better understanding of how combined psychological and pharmacological treatments work.

Thus, these findings can lead to the development of a theory-based way to integrate these interventions or maybe even to the assignment of patients to specific forms of treatment.

The results of this review paper line up nicely with neural models of depression that suggest that the interaction between subcortical (amygdala) and cortical (prefrontal) processing is of crucial importance for our understanding and treatment of depression. A large body of work on the function of the ACC has demonstrated that it may play an important role in emotional regulation, and thus may be highly relevant for understanding the development of depression. In particular the ACC is an important brain region to examine in studies on the interaction of subcortical and cortical functioning. In a seminal article, Bush, Luu, and Posner (2000) proposed that conflict monitoring in the ACC can be conceived as a bridge between subcortical emotion processing and cortical attentional control. Pereira, Oliveira, Erthal, Joffily, Mocaiber, Volchan and Pessoa (2010, in this issue) used functional magnetic resonance imaging during a target-detection task that followed the presentation of unpleasant versus neutral pictures to investigate neural correlates of behavioral interference from emotional stimuli. The results show that the emotional context modulated brain responses. Specifically the midcingulate cortex was recruited when participants performed target-detection trials during the unpleasant context and neural responses in this region mirrored the pattern of interference observed in the behavioral data. The authors conclude that the midcingulate cortex may be involved in the interaction between affective and motor signals in the brain, and may be related to defensive responses. Thus, the cingulate cortex, which has been related to the signaling of the need for attentional control upon encountering emotionally salient stimuli, might also be related to exerting behavioral control on the environment.

Whereas many depression theories have focused on the processing of negative material, the processing of positive, rewarding stimuli may be of crucial importance for our understanding of emotion regulation and stress reactivity in depressed and non-depressed

participants. Indeed, a wealth of research has investigated processing of positive information in these groups, with the depressed participants showing marked disturbances in reward processing. These disturbances may be related to negative expectations about their ability to change events (hopelessness) causing reduced initiation of behavioral control in an effort to influence the environment, resulting in a decreased in rewarding responses from that environment. The specific role of reward sensitivity in depression was investigated by Holmes and Pizzagalli (2010, in this issue), using Event Related Potentials during a task with a "no incentive" versus "reward" condition. These authors focused on action monitoring, defined as the ability to coordinate actions to maximize the likelihood of goal achievement, even following unexpected environmental changes. Previous studies have reported action monitoring dysfunction, particularly disrupted error processing (Holmes & Pizzagalli, 2008), and decreased approach-related behavior in depressed patients (for a review, see Pizzagalli, Dillon, Bogdan, & Holmes, 2009). Thus, impairments in action monitoring might be partially explained by abnormalities in incentive processing. First, the results were indicative of a generally heightened reactivity in early (automatic) stages of error processing in depression, unrelated to reward processing. Second, when rewards were available, depressed patients showed blunted responses at later stages of information processing, which are assumed to relate to conscious error awareness and subjective affective evaluative responses. As discussed previously, dysfunctional cognitive processing at later stages of information processing reliably emerge in depression. In fact, the specific psychophysiological patterns observed in these studies could be related to increased paralimbic activation and to a failure to recruit prefrontal cortex (PFC) based cognitive control, possibly due to abnormal frontocingulate connectivity. Indeed, depression has been conceptualized as a failure of dorsal areas, related to cognitive control, to regulate ventral emotion producing brain systems (Phillips, Drevets, Rauch, & Lane, 2003).

The importance of dysfunctional reward processing in depression and the relation with attentional and behavioral control systems in the brain may underlie the successful use of behavioral activation as a treatment strategy for depression, which aims at increasing environmental reinforcement and at reducing punishment. This therapeutic technique facilitates new rewarding experiences, which may enhance incentive processing. Several studies have shown the effectiveness of behavioral activation. Indeed, a recent large-scale study demonstrated a better treatment response to behavioral activation compared to cognitive therapy (Dimidjian et al., 2006).

The important role of the prefrontal cortex in this neural attention/emotion circuitry was addressed by Engels, Heller, Spielberg, Warren, Sutton, Banich and Miller (2010, this issue), who measured brain activity using fMRI during an emotion-word Stroop task, disentangling the influence of anxiety and depression, which are highly comorbid conditions. They found a right-sided asymmetrical lateralization pattern of prefrontal cortex activity for depression which was dependent on elevated comorbid anxious arousal and simultaneously low comorbid anxious apprehension. These findings not only point to the importance of the frontal cortex in cognitive control, but also highlight the important influence of comorbidity. The diversity of brain activity patterns observed in individuals with depression and anxiety might be used to match patients to specific interventions, because there is ever more research on the specificity of brain regions involved in treatment strategies for anxiety and depression (for a review, see Ressler & Mayberg, 2007).

Research on frontal related cognitive control processes (modified Stroop task) indicate that these processes further deteriorate with the experience of successive depressive episodes, which is indicative of an increasing vulnerability (Vanderhasselt & De Raedt, 2009). The framework proposed by De Raedt and Koster (2010, in this issue) attempts to explain this increasing vulnerability after multiple episodes integrating the relation among HPA axis

dysfunctions, frontal brain structures, and cognitive processes. In this framework, decreasing cognitive control processes are the crucial link between biological and cognitive factors. Understanding these interactions might also be important for the prediction of treatment outcome. Forbes, Olino, Ryan, Birmaher, Axelson, Moyles and Dahl (2010, in this issue) investigated treatment outcome prediction in adolescents with depression using fMRI during a monetary reward task, before an 8-week open trial of cognitive behavioral therapy (CBT) or CBT combined with a selective serotonin reuptake inhibitor. Severity, anxiety symptoms, and depressive symptoms decreased over treatment and the final levels of severity and anxiety symptoms were associated with pre-treatment striatal reactivity. Moreover, rate of anxiety symptom reduction was associated with greater striatal reactivity and lower medial PFC reactivity. Surprisingly however, decreases in depressive symptoms were not associated with reward-related brain function.

So far we have discussed both subcortical (amygdala) sensitivity and a prefrontal failure to exert cognitive control, the role of the ACC in the interaction between emotion and cognitive/behavioral control and in the relation between action monitoring and reward sensitivity, as important features of depression. Cognitive control, however, likely consists of a number of different sub-processes and it may be critical to understand which of these processes are impaired in depression and which may remain intact. A better understanding of the specific cognitive deficits that characterize depression may aid the development of theoretical models of this disorder and the development of effective interventions. Joormann, Nee, Berman, Jonides and Gotlib (2010, in this issue) investigated whether depression is associated with problems in controlling emotional content of short-term memory, which may result in sustained negative affect and vicious circles of negative thoughts. Importantly, these authors used an experimental paradigm that allowed them to differentiate inhibitory dysfunctions in early and later stages of processing of emotional material. Depression was not

associated with difficulties keeping irrelevant material from entering short-term memory but was associated with difficulty in removing irrelevant negative material from short-term memory, which was related to rumination. These findings may help us understand why some people recover easily from negative affect, whereas others initiate a vicious cycle of increasingly negative ruminative thinking.

Investigating cognitive processes that may underlie rumination more closely, Jones, Siegle, Muelly, Haggerty and Ghinassi (2010, in this issue) examined the degree to which depressed and never-depressed people who varied in trait rumination displayed different pupillary motility patterns during a cognitive task. Different frequencies of pupillary motility were used as an index of task-related processing versus intrinsically generated intrusive thoughts. The results suggested that engaging in intrinsic processing was related to rumination and could contribute to cognitive deficits observed in depression. Because prospective studies have shown that rumination plays a role in both the onset and maintenance of depression (Nolen-Hoeksema, 2000), trait rumination might be a key construct in understanding problems of non-response to treatment. One possibility is that a cognitive deficit in the emotion-attention control network facilitates rumination and that changes in this network might decrease rumination, but rumination can also be conceived as a dysfunctional emotion regulation strategy people use. In line with the suggestion of Borkovec (1994) that worry can be seen as a cognitive avoidance strategy, and given the overlap between worry and rumination, avoidance might be the mechanism underlying rumination in depression (De Raedt, 2006). Detailed representations or memories (e.g. traumatic past events) can be avoided by deliberately ruminating about one's depressed state in abstract terms (e.g. how should I go on with my life?). In the short term, the depressed individual does not become overwhelmed by strong emotions that are associated with these representations but in the long term, this strategy backfires since rumination undermines problem-solving (Lyubomirsky &

Nolen-Hoeksema, 1993) and prevents a true confrontation, which may be necessary for healthy emotional processing (Foa & Kozak, 1986). Difficulties inhibiting and avoidance can thus both be working mechanisms underlying rumination.

CONCLUSION

Traditionally, psychological theories and biological approaches have developed in relative isolation. Although these approaches were postulated within a biopsychosocial or a vulnerability-stress model, the precise nature of the interaction between biological and psychological factors is not well-specified. The emergence of cognitive approaches to depression, emphasizing biased processing of emotional material at the level of memory, attention, and interpretation (e.g., Williams, Watts, MacLeod, & Mathews, 1988), allows for an integration of insights from biological approaches and cognitive psychology within an affective neuroscience framework delineating vulnerability factors in depression. In this special issue we present a selection of research from different perspectives using an impressive variety of methodologies and theoretical frameworks that provide converging support for specific depression-related disturbances in neural circuitry involved in emotion generation and regulation. In this introduction we highlighted that much of this information can be interpreted with regard to vulnerability factors that predispose to the onset, maintenance, and recurrence of depression.

An important treatment implication of the reviewed studies is the idea that it may be worthwhile to more directly target cognitive and neural processes in our interventions. Recent work on cognitive bias modification, for example, has demonstrated that attentional biases can be trained and that this training leads to changes in mood and reduces reactivity to stressful events (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews and MacLeod, 2002; Wadlinger & Isaacowitz, 2008). Based on these findings, researchers have

begun to examine attentional bias training with clinical samples but no studies thus far have examined whether modifying attentional biases in depressed participants leads to improvements in emotion regulation.

Recently, studies have started to investigate the possibility of training cognitive control in depression and of examining the effects of this training on emotion regulation (e.g., Joormann, Hertel, Brozovich & Gotlib, 2005). Siegle, Thompson, Carter, Steinhauer, and Thase (2007), for example, presented preliminary data demonstrating that a brief intervention targeted at increasing cognitive control in severely depressed outpatients led to significant decreases in both depressive symptoms and rumination. Indeed, recent work by this group suggests that training in attentional control may be an effective treatment component for depression (Siegle, Ghinassi, & Thase, 2007). In this training, patients learn to selectively attend to certain sounds while ignoring irrelevant sounds. After receiving two weeks of this training, patients exhibited decreases in depressive symptoms compared to patients who received treatment as usual (Siegle et al., 2007). Notably, the training consisted of short sessions (15 minutes) that used non-affective stimuli such as the sound of birds. This suggests that cognitive control can be improved with practice and further supports the hypothesis that individual differences in cognitive control may affect emotion regulation.

Finally, recent research has begun to directly alter brain functioning using methods such as repetitive Transcranial Magnetic Stimulation (rTMS) and neurofeedback. As an illustration of such translational research, it has been shown that multi-session rTMS of the dorsolateral prefrontal cortex can be effective as a treatment of severe depression, by influencing brain activity and increasing attentional control (Vanderhasselt, De Raedt, Leyman, & Baeken, 2009; Leyman, De Raedt, Vanderhasselt, & Baeken, in press). Still, research that systematically examines the role of cognitive and biological factors for successful treatment

and prevention of depression remains scarce and we hope that this special issue will stimulate future research efforts that aim at investigating these critical questions.

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